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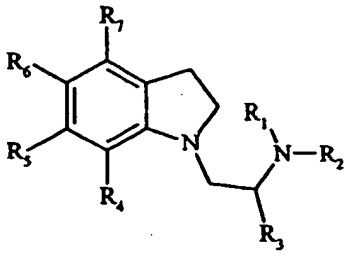
(54) Title: INDOLINE DERIVATIVES AS 5-HT2B AND/OR 5-HT2C RECEPTOR LIGANDS

(57) Abstract



(I)

For use in therapy a chemical compound of formula (I), wherein R_1 to R_3 are independently selected from hydrogen and alkyl; R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, heterocyclyl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is a substituent group other than hydrogen, and pharmaceutically acceptable salts and prodrugs thereof, particularly for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea, and especially for the treatment of obesity; chemical compounds of formula (I) other than compounds wherein R_7 is hydroxy.

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INDOLINE DERIVATIVES AS 5-HT2B AND/OR 5-HT2C RECEPTOR LIGANDS

The present invention relates to indoline derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating obesity and other disorders.

It has been recognised that obesity is a disease process influenced by environmental factors in which the traditional weight loss methods of dieting and exercise need to be supplemented by therapeutic products (S. Parker, "*Obesity: Trends and Treatments*", Scrip Reports, PJB Publications Ltd, 1996).

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m^2, and obesity as a BMI greater than 30 kg/m^2. There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

Compounds marketed as anti-obesity agents include Orlistat (Reductil®) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhoea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase

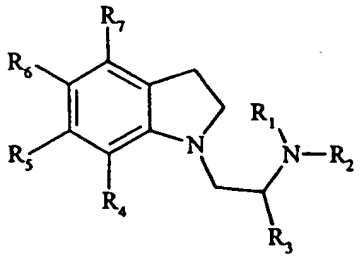
blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors fenfluramine (Pondimin®) and dexfenfluramine (Redux™) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve abnormalities associated with their use. There is therefore a need for the development of a safer anti-obesity agent.

The non-selective 5-HT_{2C} receptor agonists/partial agonists m-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP) have been shown to reduce food intake in rats (G.A. Kennett and G. Curzon, *Psychopharmacol.*, 1988, **96**, 93-100; G.A. Kennett, C.T. Dourish and G. Curzon, *Eur. J. Pharmacol.*, 1987, **141**, 429-435) and to accelerate the appearance of the behavioural satiety sequence (S.J. Kitchener and C.T. Dourish, *Psychopharmacol.*, 1994, **113**, 369-377). Recent findings from studies with mCPP in normal human volunteers and obese subjects have also shown decreases in food intake. Thus, a single dose of mCPP decreased food intake in female volunteers (A.E.S. Walsh *et al.*, *Psychopharmacol.*, 1994, **116**, 120-122) and decreased the appetite and body weight of obese male and female subjects during subchronic treatment for a 14 day period (P.A. Sargeant *et al.*, *Psychopharmacol.*, 1997, **133**, 309-312). The anorectic action of mCPP is absent in 5-HT_{2C} receptor knockout mutant mice (L.H. Tecott *et al.*, *Nature*, 1995, **374**, 542-546) and is antagonised by the 5-HT_{2C} receptor antagonist SB-242084 in rats (G.A. Kennett *et al.*, *Neuropharmacol.*, 1997, **36**, 609-620). It seems therefore that mCPP decreases food intake via an agonist action at the 5-HT_{2C} receptor.

Other compounds which have been proposed as 5-HT_{2C} receptor agonists for use in the treatment of obesity include the substituted 1-aminoethyl indoles disclosed in EP-A-0655440. CA-2132887 and CA-2153937 disclose that tricyclic 1-aminoethylpyrrole derivatives and tricyclic 1-aminoethylpyrazole derivatives bind to 5-HT_{2C} receptors and may be used in the treatment of obesity. WO-A-98/30548 discloses aminoalkylindazole compounds as 5-HT_{2C} agonists for the treatment of CNS diseases and appetite regulation disorders.

It is an object of this invention to provide selective, directly acting $5HT_2$ receptor ligands for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide directly acting ligands selective for $5\text{-}HT_{2B}$ and/or $5\text{-}HT_{2C}$ receptors, for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide selective, directly acting $5\text{-}HT_{2C}$ receptor ligands, preferably $5\text{-}HT_{2C}$ receptor agonists, for use in therapy and particularly for use as anti-obesity agents.

According to the present invention there is provided for use in therapy a chemical compound of formula (I):



(I)

wherein:

R_1 to R_3 are independently selected from hydrogen and alkyl;

R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, heterocyclyl, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is a substituent group other than hydrogen,

and pharmaceutically acceptable salts and prodrugs thereof.

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5, C_6 or C_7. Where acyclic, the alkyl group is preferably C_1 to C_{10}, more preferably C_1 to

C_6, more preferably methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl), more preferably methyl.

As used herein, the term "lower alkyl" means methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl).

As used herein, the term "aryl" means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteroatom, such as pyridyl, pyrrolyl, furanyl and thienyl.

As used herein the term "heterocyclyl" means a saturated 4, 5, 6 or 7-membered ring (preferably a 5 or 6-membered ring) containing 1, 2 or 3 heteroatoms (preferably 1 or 2 heteroatoms) selected from O, S and N (preferably from O and N).

The alkyl, aryl and heterocyclyl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include:

carbon-containing groups such as

- alkyl,
- aryl,
- arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen-containing groups such as

- haloalkyl (e.g. trifluoromethyl);

oxygen-containing groups such as

- alcohols (e.g. hydroxy, hydroxyalkyl, aryl(hydroxy)alkyl),
- ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl),
- aldehydes (e.g. carboxaldehyde),
- ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl),
- acids (e.g. carboxy, carboxyalkyl),
- acid derivatives such as esters

(e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl),

amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl),

carbamates (e.g. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylaminocarbonyloxy)

and ureas (e.g. mono- or di-alkylaminocarbonylamino or arylaminocarbonylamino);

nitrogen-containing groups such as

amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl),

azides,

nitriles (e.g. cyano, cyanoalkyl),

nitro;

sulfur-containing groups such as

thiols, thioethers, sulfoxides and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl);

and heterocyclic groups containing one or more, preferably one, heteroatom, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazoiinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl,

morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by one or more alkyl groups.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine, chlorine or bromine radical.

As used herein the term "prodrug" means any pharmaceutically acceptable prodrug of the compound of formula (I).

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are fumaric, hydrochloric, hydrobromic, phosphoric, succinic, sulfuric and methanesulfonic acids. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminium salts.

Preferably, the compounds of formula (I) are selected from compounds in which R_1 is the same as R_2. Preferably, R_1 and R_2 are both hydrogen. In an embodiment of the invention, R_1 is hydrogen and R_2 is substituted or unsubtituted alkyl, preferably lower

alkyl, preferably methyl. Where substituted, the substituent group is preferably an aryl group, preferably phenyl, pyridyl or thienyl.

Preferably, the compounds of formula (I) are selected from compounds in which R_3 is alkyl, preferably lower alkyl, preferably methyl. Where R_3 is alkyl, the carbon atom to which R_3 is attached is an asymmetric carbon atom. It is preferred that this asymmetric carbon atom is in the (*S*)-configuration, wherein the stereochemical assignment is defined with respect to a compound wherein R_3 is an unsubstituted alkyl group.

R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, heterocyclyl (including aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, hexahydroazepinyl, tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, tetrahydrothienyl and tetrahydrothiopyranyl), alkoxy (including arylalkoxy), aryloxy, alkylthio, arylthio, alkylsulfoxyl, alkylsulfonyl, arylsulfoxyl, arylsulfonyl, amino, monoalkylamino, dialkylamino, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino, wherein at least one of R_4 to R_7 is other than hydrogen.

In an embodiment of the invention R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, alkoxy (including arylalkoxy), aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl, wherein at least one of R_4 to R_7 is other than hydrogen.

It is preferred that the compounds of formula (I) are selected from compounds in which R_4 is selected from halogen (preferably fluoro) and hydrogen. R_4 is preferably hydrogen.

It is preferred that the compounds of formula (I) are selected from compounds in which R_5 is selected from halogen, alkyl, aryl, alkoxy, alkylthio, monoalkylamino and dialkylamino. Preferably R_5 is selected from halogen, alkyl, alkoxy, alkylthio,

monoalkylamino and dialkylamino, and more preferably from halogen (preferably chloro, bromo and fluoro, more preferably chloro and bromo), alkyl (preferably haloalkyl and more preferably trifluoromethyl), alkoxy (preferably lower alkoxy) and alkylthio (preferably lower alkylthio).

It is preferred that the compounds of formula (I) are selected from compounds in which R_6 is selected from halogen and hydrogen. Preferably R_6 is selected from halogen (preferably fluoro, chloro and bromo, and more preferably fluoro).

It is preferred that the compounds of formula (I) are selected from compounds in which R_7 is hydrogen.

In a preferred embodiment, the compounds of formula (I) are selected from 1-(6-chloro-5-fluoroindolin-1-yl)-2-propylamine, 1-(5,6-difluoroindolin-1-yl)-2-propylamine, 1-(6-bromo-5-fluoroindolin-1-yl)-2-propylamine, 1-(6-bromoindolin-1-yl)-2-propylamine, 1-(6-chloroindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-trifluoromethylindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-methylthioindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-iodoindolin-1-yl)-2-propylamine, 1-(5-fluoro-6-ethylthioindolin-1-yl)-2-propylamine, 1-(-5-fluoro-6-methylindolin-1-yl)-2-propylamine, 1-(6-methylthioindolin-1-yl)-2-propylamine, 1-(6-ethylthioindolin-1-yl)-2-propylamine, 1-(6-trifluoromethylindolin-1-yl)-2-propylamine, 1-(6-methoxyindolin-1-yl)-2-propylamine, 1-(6-propylthioindolin-1-yl)-2-propylamine, 1-(6-isopropylthioindolin-1-yl)-2-propylamine, 2-(6-chloroindolin-1-yl)-1-ethylamine, 2-(6-bromoindolin-1-yl)-1-ethylamine, 1-(5-chloroindolin-1-yl)-2-propylamine, 1-(5-fluoroindolin-1-yl)-2-propylamine and 1-(6-methylindolin-1-yl)-2-propylamine, and particularly the (*S*)-enantiomers thereof.

The compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. The compounds can be, for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

In a preferred embodiment of the invention, a compound of formula (I) is in the form of its (*S*)-enantiomer, substantially free of its (*R*)-enantiomer. As used herein, the

term "substantially free of its (*R*)-enantiomer" means that a composition comprising a compound of formula (I) contains a greater proportion of the (*S*)-enantiomer of the compound of formula (I) in relation to the (*R*)-enantiomer of the compound of formula (I). In a preferred embodiment of the present invention, the term "substantially free of its (*R*)-enantiomer", as used herein, means that the composition contains at least 90 % by weight of the (*S*)-enantiomer and 10 % by weight or less of the (*R*)-enantiomer. In a further preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains at least 99 % by weight of the (*S*)-enantiomer and 1 % or less of the (*R*)-enantiomer. In another preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains 100 % by weight of the (*S*)-enantiomer. The above percentages are based on the total amount of a compound of formula (I) present in the composition.

According to a further aspect of the invention, there is provided a compound of formula (I), *per se*, wherein R_7 is a substituent other than hydroxy. In a preferred embodiment, there is provided a compound of formula (I), *per se*, wherein R_7 is hydrogen.

The compounds of formula (I) may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_2 receptor function. The compounds may act as receptor agonists or antagonists. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_{2B} and/or 5-HT_{2C} receptor function. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders where a 5-HT_{2C} receptor agonist is required.

The compounds of formula (I) may be used in the treatment or prevention of central nervous disorders such as depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood,

aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa or premenstrual tension; damage of the central nervous system such as by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases such as encephalitis or meningitis; cardiovascular disorders such as thrombosis; gastrointestinal disorders such as dysfunction of gastrointestinal motility; diabetes insipidus; and sleep apnea.

According to a further aspect of the invention, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of the above-mentioned disorders. In a preferred embodiment, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of obesity.

According to a further aspect of the invention, there is provided a method of treatment (including prophylaxis) of a disorder selected from the group consisting of the above-mentioned disorders comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I). In a preferred embodiment, there is provided a method of treatment (including prophylaxis) of obesity.

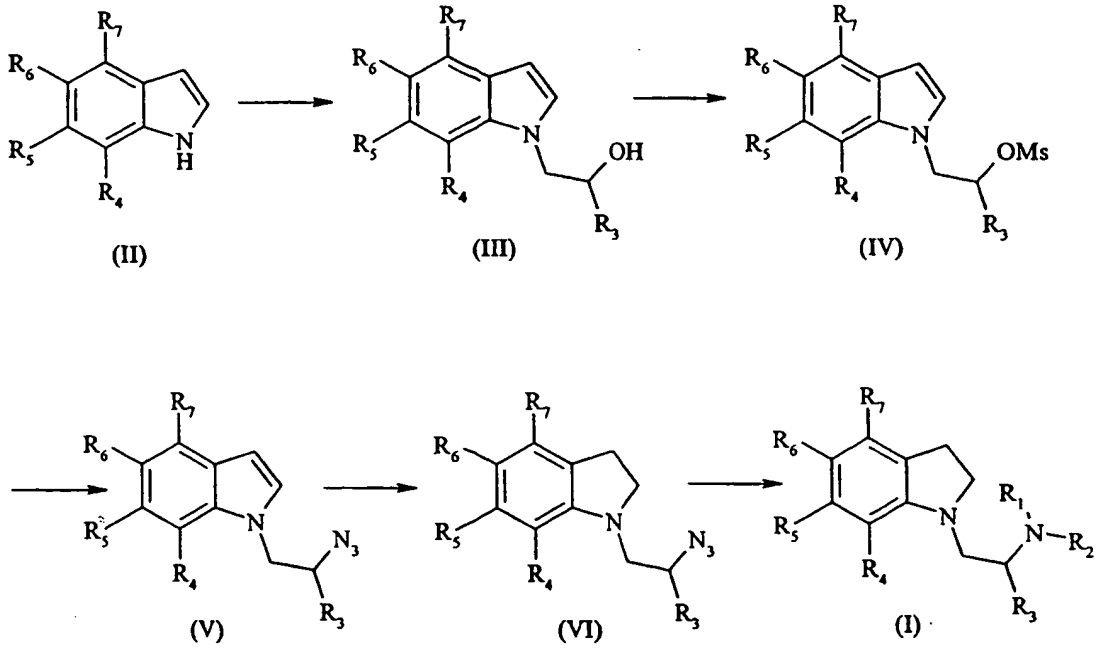
According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

According to a further aspect of the invention, there is provided a method of preparing a compound of formula (I).

Compounds of formula (I) may be prepared according to Reaction Scheme 1 below. R_1 to R_7 are as previously defined. The (indolyl)-alkylethanol (III) may be prepared by reaction of the substituted indole (II) with an alkylene oxide in the presence of a strong base such as sodium hydride in a solvent such as tetrahydrofuran. The corresponding azido derivative (V) can be formed in a two step procedure from the

derivative (III) by formation of the mesylate (IV), obtained by reaction of (III) with methanesulfonyl chloride in the presence of a base such as triethylamine, and subsequent treatment of the mesylate (IV) with sodium azide in a solvent such as dimethyl formamide. The indoline (VI) can then be obtained by reduction of the indole (V) with, for example, sodium cyanoborohydride in acetic acid as solvent. The resultant azidoindoline (VI) can then be reduced to a compound of formula (I) ($R_1 = R_2 = H$) using for example a mixture of zinc powder and nickel chloride hexahydrate in a solvent such as tetrahydrofuran or alternatively using hydrogen over a catalyst such as platinum(IV)oxide in a solvent such as ethanol.

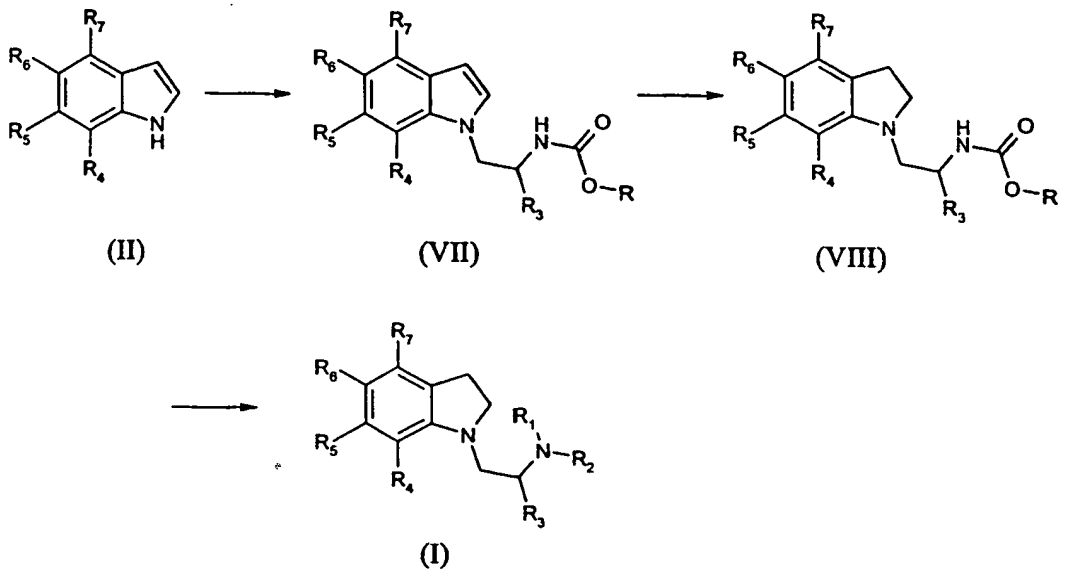
Reaction Scheme 1



Alternatively compounds of the invention may be prepared according to Reaction Scheme 2 below. The carbamate (VII) may be formed by reaction of the indole (II) with a carbamoylethylsulfonate in the presence of a strong base such as potassium hydroxide in a solvent such as methyl sulfoxide. The indoline (VIII) may be obtained by reaction of the indole (VII) with a reducing agent such as sodium cyanoborohydride or a tetra-alkylammonium borohydride. The compounds of formula

(I) ($R_1 = R_2 = H$) may be prepared by deprotection of the amine function of the indoline (VIII).

Reaction Scheme 2



(II) (VII) (VIII) (I)

If, in any of the other processes mentioned herein, the substituent group R_4, R_5, R_6 or R_7 is other than the one required, the substituent group may be converted to the desired substituent by known methods. The substituents R_4, R_5, R_6 or R_7 may also need protecting against the conditions under which the reaction is carried out. In such a case, the protecting group may be removed after the reaction has been completed.

The compounds of formula (I) (R_1 and/or R_2 = alkyl) may be prepared from compounds of formula (I) ($R_1 = R_2 = H$) by standard methods such as reductive alkylation with an appropriate aldehyde or ketone in the presence of a reducing agent such as sodium triacetoxyborohydride, formic acid or sodium cyanoborohydride.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating

the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from basic compounds.

The compositions comprising a compound of formula (I) may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of formula (I) may be formulated for oral, buccal, intranasal, parenteral (*e.g.*, intravenous, intramuscular or subcutaneous) transdermal or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.* pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.* lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.* magnesium stearate, talc or silica); disintegrants (*e.g.* potato starch or sodium starch glycollate); or wetting agents (*e.g.* sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.* sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.* lecithin or acacia); non-aqueous vehicles (*e.g.* almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.* methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of formula (I) may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles,

and may contain formulating agents such as suspending, stabilizing and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, *e.g.* sterile pyrogen-free water, before use.

The active compounds of formula (I) may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of formula (I) are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of formula (I) for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (*e.g.*, obesity) is 0.1 to 500 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

EXPERIMENTAL

Assay Procedures

1. Binding to serotonin receptors

The binding of compounds of formula (I) to serotonin receptors was determined *in vitro* by standard methods. The preparations were investigated in accordance with the assays given hereinafter.

Method (a): For the binding to the 5-HT_{2C} receptor the 5-HT_{2C} receptors were radiolabeled with [^{3}H]-5-HT. The affinity of the compounds for 5-HT_{2C} receptors in a CHO cell line was determined according to the procedure of D. Hoyer, G. Engel and H.O. Kalkman, *European J. Pharmacol.*, 1985, **118**, 13-23.

Method (b): For the binding to the 5-HT_{2B} receptor the 5-HT_{2B} receptors were radiolabeled with [^{3}H]-5-HT. The affinity of the compounds for human 5-HT_{2B} receptors in a CHO cell line was determined according to the procedure of K. Schmuck, C. Ullmer, P. Engels and H. Lubbert, *FEBS Lett.*, 1994, **342**, 85-90.

Method (c): For the binding to the 5-HT_{2A} receptor the 5-HT_{2A} receptors were radiolabeled with [^{125}I]-DOI. The affinity of the compounds for 5-HT_{2A} receptors in a CHO cell line was determined according to the procedure of D. J. McKenna and S. J. Peroutka, *J. Neurosci.*, 1989, **9**, 3482-90.

The thus determined activity of compounds of formula (I) is shown in Table 1.

Table 1

Compound	K_i (2C)	K_i (2B)	K_i (2A)
Example 1	357 nM	113 nM	405 nM
Example 10	55 nM	138 nM	252 nM
Example 12	77 nM	42 nM	1092 nM
Example 13	122 nM	175 nM	461 nM
Example 22	260 nM	92 nM	325 nM
Example 24	235 nM	148 nM	1866 nM
Example 25	63 nM	22 nM	156 nM
Example 26	1156 nM	761 nM	1262 nM
Example 50	61 nM	159 nM	332 nM
Example 51	165 nM	140 nM	1113 nM

2. Functional activity

The functional activity of compounds of formula (I) was assayed using a Fluorimetric Imaging Plate reader (FLIPR). CHO cells expressing the human 5-HT_{2C} or human 5-HT_{2A} receptors were counted and plated into standard 96 well microtitre plates on the day before testing to give a confluent monolayer. The cells were then dye loaded with the calcium sensitive dye, Fluo-3-AM. Unincorporated dye was removed using an automated cell washer to leave a total volume of 100 µL/well of assay buffer (Hanks balanced salt solution containing 20 mM Hepes and 2.5 mM probenecid). The drug (dissolved in 50 µL of the assay buffer) was added at a rate of 70 µL/sec to each well of the FLIPR 96 well plate during fluorescence measurements. The measurements were taken at 1 sec intervals and the maximum fluorescent signal was measured (approx 10-15 secs after drug addition) and compared with the response produced by 10 µM 5-HT (defined as 100%) to which it was expressed as a percentage response (relative efficacy). Dose response curves were constructed using Graphpad Prism (Graph Software Inc.).

The thus determined activity of compounds of formula (I) is shown in Table 2.

Table 2

Compound	h5-HT_{2A}		h5-HT_{2C}	
	EC_{50} (nM)	Relative Efficacy (%)	EC_{50} (nM)	Relative Efficacy (%)
Example 2	1000	63	100	77
Example 9	5600	52	253	89
Example 10	2215	49	125	62
Example 12	2409	49	230	59
Example 13	386	72	75	74
Example 14	3700	55	2120	71
Example 15	10000	12	4700	14
Example 16	793	52	9	80
Example 17	7500	40	616	76
Example 18	-	7	870	27
Example 19	-	21	3800	34
Example 20	-	17	750	68
Example 22	2567	57	83	87
Example 23	1351	34	354	76
Example 24	3651	33	131	72
Example 25	1244	57	21	81
Example 27	1976	41	233	75
Example 28	1537	63	238	75
Example 29	3167	18	503	68
Example 30	72	88	0.1	95
Example 31	314	72	2	92
Example 32	1516	26	611	63
Example 33	2933	51	257	75
Example 35	10000	30	727	51
Example 37	2733	27	391	69
Example 38	2562	26	320	63
Example 39	260	75	4	87
Example 40	836	64	3	95
Example 41	10000	-	67	83
Example 42	4197	43	54	88

Example 47	10000	5	3545	33
Example 49	10000	5	5478	69
Example 50	4080	25	38	78
Example 51	1893	45	36	88
Example 53	2312	20	266	86
Example 60	10000	-	36	81
Example 61	2184	49	26	68
Example 62	10000	-	329	54
Example 64	10000	30	303	66

3. Efficacy

The efficacy of 5-HT_{2C} agonists was assessed for ability to induce a specific syndrome.

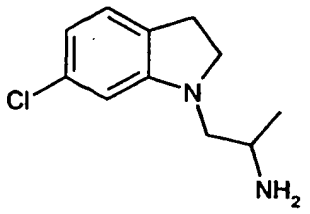
The 5-HT_{2C} syndrome is a rapid screening method to assess the *in vivo* efficacy of 5-HT_{2C} agonists through their ability to induce three specific behaviours in rats. The animals are dosed with either a positive control (mCPP), test compound or vehicle, either sub-cutaneously or p.o.. The animals are observed on an open bench, typically 30, 60 and 180 minutes and the degree of syndrome is assessed over a two minute period on a scale of 0-3 depending on the presence and severity of splayed limbs, hunched posture and retro-pulsion, the three specific behaviours which constitute the syndrome. Data is analysed using Kruskal-Wallis Analysis of Variance followed with appropriate post-hoc tests. All statistical analysis are conducted using Excel version 7.0 (Microsoft Corp.) and Statistica version 5.0 (Statsoft, Inc.).

The thus determined activity of Example 1 indicates that after a dose of 30 mg/kg s.c. the compound maintains significant pharmacological efficacy for at least 180 minutes.

Synthetic Examples

General Method A:

Example 1: (*RS*)-1-(6-Chloroindolin-1-yl)-2-propylamine hydrochloride



Step (a): (*RS*)-1-(6-Chloroindol-1-yl)-2-propanol (1a)

To a stirred suspension of sodium hydride (60%, 1.26 g, 31.6 mmol) in tetrahydrofuran (30 mL) at 0 °C under Ar was added dropwise a solution of 6-chloroindole (4.0 g, 26 mmol) in tetrahydrofuran (30 mL). The mixture was stirred for 1 h and (*RS*)-propylene oxide (3.7 mL, 53 mmol) was added. The mixture was warmed to room temperature, stirred for 48 h and partitioned between aqueous ammonium chloride solution (100 mL) and ether (3 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; ethyl acetate-hexane (1:9)] to give the product (2.78 g, 50% yield) as a pale yellow oil. Data for the compounds produced using General Method A, step (a) are listed in Table 3.

Step (b): (*RS*)-1-(2-Azidopropyl)-6-chloroindole (1b)

To a stirred solution of (*RS*)-1-(6-chloroindol-1-yl)-2-propanol (2.5 g, 11.9 mmol), dichloromethane (60 mL) and triethylamine (1.8 mL, 13 mmol) at 0 °C was added dropwise methanesulfonyl chloride (1 mL, 13 mmol). The mixture was warmed to room temperature, stirred for 1 h and partitioned between brine (50 mL) and dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (magnesium sulfate) and concentrated *in vacuo* to give a pale yellow

solid (3.3 g), which was added to a stirred mixture of dimethyl formamide (30 mL) and sodium azide (1.1 g, 17 mmol). The mixture was heated to 70 °C, stirred for 16 h, cooled to room temperature and partitioned between brine (50 mL) and ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; ether-hexane (1:9)] to give the product (1.7 g, 63% yield) as a colourless oil. Data for (1b) are included in Table 4 with the data for other compounds produced using General Method A, step (b).

Step (c): *(RS)*-1-(2-Azidopropyl)-6-chloroindoline (1c)

To a stirred solution of (*RS*)-1-(2-azidopropyl)-6-chloroindole (1.5 g, 6.4 mmol) in acetic acid (25 mL) at 5 °C was added portionwise sodium cyanoborohydride (1.2 g, 19 mmol). The mixture was warmed to room temperature, stirred for 16 h and partitioned between ether (100 mL) and aqueous sodium bicarbonate solution (4 x 100 mL). The organic layer was washed (brine), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2:ethyl acetate-hexane (1:9)] to give the product (1.39 g, 92% yield) as a pale yellow oil. Data for (1c) are included in Table 5 with the data for other compounds produced using General Method A, step (c).

Step (d): *(RS)*-1-(6-Chloroindolin-1-yl)-2-propylamine hydrochloride (1)

To a stirred solution of (*RS*)-1-(2-azidopropyl)-6-chloroindoline (0.92 g, 1.8 mmol) in tetrahydrofuran (70 mL) at 0 °C under Ar was added portionwise a mixture of Zinc powder (1.3 g, 20 mmol) and nickel chloride hexahydrate (6.8 g, 28 mmol). The mixture was warmed to room temperature, stirred for 16 h, and partitioned between water (50 mL) and ethyl acetate (3 x 30 mL). The combined organic extracts were washed (brine), dried (magnesium sulfate) and concentrated *in vacuo* to give a pale brown oil. The oil was dissolved in a mixture of ether (10 mL) and dichloromethane (20 mL) and the solution was cooled to 0 °C. Ethereal hydrogen chloride solution (1.0 M, 3.9 mL, 3.9 mmol) was added dropwise and the mixture stirred at room temperature for 10 min. The mixture was concentrated *in vacuo* and recrystallised (2-propanol) to

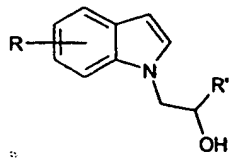
give the product (0.42 g, 38% yield) as a pale pink solid. Data for (1) are included in Table 6 with the data for other compounds produced using General Method A, step (d).

Alternative Step (d): *(RS)*-1-(6-Methoxyindolin-1-yl)-2-propylamine hydrochloride (2)

A mixture of (*RS*)-1-(2-azidopropyl)-6-methoxyindoline (0.27 g, 1.1 mmol), ethanol (10 mL) and platinum(IV)oxide (0.01 g, 0.04 mmol) was stirred under hydrogen for 12 h. The mixture was filtered through a pad of Celite® and concentrated *in vacuo* to give a pale yellow oil, which was dissolved in ether (5 mL) and cooled to 0 °C. Ethereal hydrogen chloride solution (1.0 M, 1.1 mL, 1.1 mmol) was added dropwise and the mixture was was concentrated *in vacuo* and recrystallised (2-propanol) to give the product (0.18 g, 64%) as a pale blue solid. Data for (2) are included in Table 6 with the data for other compounds produced using General Method A, step (d).

The compounds shown in Tables 3, 4, 5 and 6 were prepared using General Method A from (*RS*)-propylene oxide, (*R*)-propylene oxide, (*RS*)-1,2-epoxybutane and fumaric acid as appropriate.

Table 3: Indoles prepared using General Method A, step (a)

No		Data
1a	R = 6-Cl R' = Me	IR ν_{max} (film)/cm^{-1} 3387, 2972, 2931, 1711, 1608, 1506, 1465, 1396, 1377, 1339, 1320, 1243, 1200, 1139, 1091, 1065, 938, 908, 898, 839, 805, 721, 673, 605 and 492; NMR δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6 Hz), 3.98 (1H, dd, *J* 8, 14.5 Hz), 4.12 (1H, dd, *J* 3.5, 14.5 Hz), 4.19 (2H, m), 6.49 (1H, d, *J* 3.5 Hz), 7.07 (1H, dd, *J*, 2, 8.5 Hz), 7.13 (1H, d, *J* 3.5 Hz), 7.36 (1H, d, *J* 2 Hz), 7.52 (1H, d, *J* 8.5 Hz).
2a	R = 6-OMe R' = Me	NMR δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6 Hz), 3.86 (3H, s), 3.96 (1H, dd, *J* 14 and 8 Hz), 4.08 (1H, dd, *J* 14 and 4 Hz), 4.15 (1H, m), 6.43 (1H, d, *J* 3 Hz), 6.82 (2H, m), 7.01